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08/230,012	4/19/94	MARSCHEL, A	263PCTR7644U

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EXAMINER	
ART UNIT	PAPER NUMBER
	12/28/25

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4-19-94 (3-3-94) ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 17-20, 22, 23, and 25-39 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-16, 21, and 24 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 17-20, 22, 23, and 25-39 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

AM
08/230,012

Applicant's arguments; filed 3/3/94 in the parent application and entered per a request in Paper No. 24, filed 4/19/94; have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either newly applied or reiterated. It is noted that the discovery of new art has resulted in the rejection of certain claims that were previously indicated as being allowable. They constitute the complete set presently being applied to the instant application.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present title is directed only to analysing which is a method of analysis whereas in contrast methods of preparation and analysis as well as apparati are claimed. Additionally, the title is overly broad as compared to the claimed invention.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

Claim 19 cites several specific steps in a method for generating an array of oligonucleotides within discrete cells of a support material. Consideration of the instant disclosure as well as all of the priority documents cited instantly has revealed that there is no written description of the distinct steps now given in claim 19. Specifically, there is no written basis for separate steps b)-d) wherein a first, second, and third set of cell locations are each separately coupled with a nucleotide with continuation of this sequence of coupling steps until the desired array is generated. The closest disclosure found is page 17, line 17, through page 18, line 19, where a synthesis cycle is described but without any description of sets of cell locations or steps of synthesis as presently given in instant claim 19. It is noted that a British Patent Application is cited on page 17, lines 15-16, but that this citation is cited as being directed to the preparative technique given on page 16, line 25, through page 17, line 14, which also lacks written basis for said steps of instant claim 19. This lack of written description supports this NEW MATTER rejection of claims 19, 20, 22, 23, and 38.

Claims 19, 20, 22, 23, and 38 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the above objection to the specification.

Claims 17, 18, 25-37, and 39 are rejected, as discussed below, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly

claim the subject matter which applicant regards as the invention.

Claim 17 is vague and indefinite due to the presence of the either of the phrases "defined sequence" or "defined sequences" in lines 3, 6, and 7. Claims 18, 25-37, and 39 also contain one of these phrases either directly or via dependence from other claims and thus are also vague and indefinite. It is firstly noted that the word "defined" is not itself defined anywhere in the specification. Without such definition someone of ordinary skill in the art reading this word must rely on normal usage of these phrases for their meaning. It is noted that applicants have not pointed to any art recognized definition of these phrases. One interpretation of these phrases is that they mean that each and every nucleotide of said sequence or sequences is known, that is a detailed spelled out sequence. It is noted that applicants have relied on this interpretation in arguing against previously applied prior art rejections based on Brigati et al. and Saiki et al. in that they do not recite "defined" sequences. Another interpretation of these phrases is that the sequences are defined by their source of procurement. It is deemed reasonable to distinguish human genomic DNA, for example, from E. coli genomic DNA as defined by their source. Brigati et al. discusses the DNA from various viruses in the last sentence of the abstract as being visualized in autopsy tissues. Figure 5 therein on page 42 shows the visualization of adenovirus DNA in A549 cells. Clearly, adenovirus DNA is distinguished and therefore "defined"

as being different from the genomic DNA in the A549 cells. Without a disclosed definition of the word "defined" as it relates to sequences it is deemed reasonable to include interpretations of "defined" that are broader than only meaning sequences with a spelled out detailed base sequence. It is additionally noted that many strains of viruses have been completely sequenced including adenovirus strains. If applicant wishes the claim meaning of "defined sequence(s)" to be limited to a sequence or sequences where every nucleotide base is known then clearer wording in the claims is needed to specify this. It is insufficient to merely argue for a specific meaning of a phrase since such an argument will not be printed as part of a patent that may be issued from the instant application, thus leaving the claims in any such patent still vague and indefinite if worded as presently worded.

PRIORITY DATE CONSIDERATION FOR DISCLOSURE OF THE INSTANT CLAIMS:

Consideration of the disclosure in the oldest priority document; Great Britain 8810400.5, filed 5/3/88; revealed that written basis is present for instant claims 17, 18, 26, 27, 32-36, and 39. Therefore priority is granted to 5/3/88 for instant claims 17, 18, 26, 27, 32-36, and 39. It is noted that the synthetic steps of instant claim 19 is not disclosed in said earliest priority document because there is no such detailed set of steps given therein. Therefore instant claim 19 and claims dependent therefrom are not granted priority to said oldest priority document. Additionally, there is no written description

of arrays containing attached oligonucleotides of different lengths within the same array but rather only a single chosen length for all oligonucleotides within each array. Therefore instant claims 25 and those dependent therefrom are not granted priority to said earliest priority document. Lastly, the 1M-5M TMACl concentrations cited in instant claim 37 have no written basis in said oldest priority document thus preventing the granting of priority to said priority document for instant claim 37. Regarding the priority document; PCT/GB89/00460, filed 5/2/89, consideration of its disclosure revealed added disclosure is present directed to arrays containing attached oligonucleotides of different length on each array. Therefore priority is granted to additional instant claims 25 and 28-31 to said PCT, filed 5/2/89. The parent application serial number 07/573,317; filed 9/28/90 and now abandoned; does not add disclosure over the PCT application. The remaining claims; 19, 20, 22, 23, 37, and 38 are granted priority to the C-I-P application of said parent which is serial number 07/695,682, filed 5/3/91, except that for claims 19 and claims dependent therefrom a rejection is summarized above regarding NEW MATTER.

SUMMARY of priority dates:

5/3/88: claims 17, 18, 26, 27, 32-36, and 39

5/2/89: claims 25 and 28-31

5/3/91: claims 19, 20, 22, 23, 37, and 38

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under

this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 25 and 39 are rejected under 35 U.S.C. § 102(b) and (e) as being anticipated by Mundy.

Example 2 of Mundy in columns 10-13, depicted in Figure 8, discloses the preparation of membrane sections with four spots on each section, two spots with pBR322 DNA attached and two spots with pAT153 DNA attached. These spots are available for hybridization as demonstrated by the hybridization of a 20-mer probe that is radioactively labeled with ^{32}P. The plasmid DNA in the spots have a defined sequence either defined by their source or well known well known in the art as for pBR322, for example, or as prepared as discussed in Mundy for pAT153. Mundy discloses the analysis of the labeled probe via various reactions which also reads on the instant analysis use of the instant arrays. Thus, the array of Mundy contains oligonucleotides of different sequence and length. See the plasmid description in column 10, lines 54-60. The above Mundy disclosure reads on the instant claims in that a support has a surface on which is attached oligonucleotides of defined and different sequences in discrete

spots or cell location. It is noted that there is no clear definition of oligonucleotides that defines length limitations that distinguishes the plasmids of Mundy from oligonucleotides cited in the claims.

Claims 25-28, 32, and 39 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Saiki et al.

Figure 2 on page 164 of Saiki et al. shows three membrane strips. Consideration of the Figure 2 legend reveals that these 3 strips were prepared identically with nucleic acids spotted as shown with nucleic acids designated as AA thru AC. These spotted nucleic acids are prepared from blood samples of known β-globin genotypes which results in their being of different sequences but defined by said genotypes. Each strip is then hybridized with a different ^{32}P labeled probe which is designated 19C, 19S, and 19A, respectively. As shown in Figure 2 each strip results in the labeled probes hybridizing selectively to the spots thereon thus analyzing the hybridization of said labeled probes. The strips read on the above listed apparatus claims due to the presence of cell locations or spots with different sequence polynucleotides and also reads on the above listed method claims due to the analysis of hybridization of the labeled probe. It is noted that the instant claims cite oligonucleotides as being attached on the arrays but do not define the length of these oligonucleotides such as to prevent the β-globin nucleic acids of Saiki et al. from being reasonably interpreted as oligonucleotides without further claim wording to clearly

distinguish the nucleic acids disclosed in Saiki et al. from the oligonucleotides as instantly claimed. In other words, the instant specification lacks an upper size limit to oligonucleotides attached to arrays.

Claims 25-27, 30, 33, 34, and 39 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brigati et al.

Brigati et al. disclose the in-situ hybridization of probes onto glass coverslips prepared with immobilized cells infected with various viruses as discussed starting on page 35, first column, in the section entitled "Coverslip and Slide Preparation" through page 39, second column. Figures 4-6 show results that document the hybridizability of labeled probes to certain virally infected cells and not others nor to cellular genomic DNA immobilized also within cells of the array. These constructs read on the instantly claimed apparati given a lack of a clear definition of the upper size limit of what is meant by the term "oligonucleotide". It is noted that the instant claims cite oligonucleotides as being attached on the arrays but do not define the length of these oligonucleotides such as to prevent the viral nucleic acids of Brigati et al. from being reasonably interpreted as oligonucleotides without further claim wording to clearly distinguish the nucleic acids disclosed in Brigati et al. from the oligonucleotides as instantly claimed. The random degradation of the polynucleotide that is hybridized to the immobilized array and at least partially labeled with ^{32}P is given in Brigati et al. on page 37, second column, in the section

entitled, "Preparation of hybridization probes".

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 17, 18, 25, 26, 28, 29, 31, 32, 35, 37, and 39 are rejected under 35 U.S.C. § 103 as being unpatentable over Hafeman et al., taken in view of Macevicz regarding instant claims 29 and 35., and taken in view of Wood et al. regarding instant claim 37.

The invention is directed to apparati arrays with either covalently attached or more broadly attached distinct oligonucleotides at separate locations on the array for hybridization assays. Methods of analysis via hybridization between immobilized oligonucleotides and an analyte whose sequence is being determined as also claimed.

Hafeman et al. disclose an apparatus and methods of analysis of liquid samples performed on a semiconductor support in the SUMMARY OF THE INVENTION section in column 2. This section

states that a plurality of analytes are analyzed using a number of isolated electrodes. This simultaneous determination of multiple analytes is additionally summarized in column 21, lines 3-25. A generic list of receptors that may be separately immobilized on the surface of a support for analysis is given in column 10, lines 26-34. Specifically, complementary nucleic acids as receptors for the detection of nucleic acid analytes via hybridization assays is discussed in column 13, lines 51-62. Since the probes that are immobilized on the support are generically cited as hybridization probes, this also suggests and motivates generic hybridization probe practice as is well known in the art but is also substantiated by Macevicz at column 2, lines 30-68, and at column 6, lines 35-38, which discloses small oligonucleotide probes as small as 8 nucleotides in length used for sequence determination. It is noted that these small probes are also disclosed in the abandoned parent application of Macevicz, filed 4/25/88, which is deemed therefore to be the date of disclosure of these probe length limitations as is also instantly claimed in claims 29 and 35. Additionally, the generic usage of molar concentrations of tetramethylammonium chloride (instant claim 37) in hybridization assays using oligonucleotide probes is disclosed in Wood et al. taken as a whole and as depicted in Figure 1 on page 1586 therein. A multiplicity of measurements are conducted on the electrode by the separate connection of individual electrical leads to separate pixels as discussed in column 14, lines 15-23. The motivation and

suggestion to covalently or non-covalently layers that are active in analysis of the sample analytes is given specifically in column 6, lines 62-65. These bonding suggestions are generically directed to the active components, such as nucleic acid hybridization probes discussed above, in column 7, lines 9-20. Samples are analyzed in Hafeman et al. by applying them to the apparatus followed by electrical detection of analyte binding by capacitive changes as summarized in the SUMMARY OF THE INVENTION in column 2, lines 1-52. This suggests the instant analysis methods wherein hybridization between analytes and probes on the surface. It is noted that said hybridization is an analysis of the sequence of one or more polynucleotides in the sample as is also instantly claimed and that such hybridization assays are well known to include detection of mutations such as point mutations.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to prepare semiconductor supports with surface attached nucleic acids which are array apparati as instantly claimed because Hafeman et al. discloses such supports with multiple and separate analyte pixels on its surface and suggests and motivates nucleic acid hybridization probes as a receptor for complementary nucleic acid analytes with a variety of chemical reactions for immobilization disclosed thus giving a reasonable expectation of success. The above rejected methods are also suggested as discussed above. It is also noted that Hafeman et al. is a continuation of a parent

application, filed 8/22/85, which is thus deemed to be the date of disclosure of the above discussed apparati and methods by Hafeman et al. The limitations of instant claims 29, 35, and 37 are motivated by the generic hybridization assay disclosure of Hafeman et al. which thus is deemed to suggest the practice of Macevicz or Wood et al. as discussed above.

Claims 19, 22, 23, and 38 are rejected under 35 U.S.C. § 103 as being unpatentable over Fodor et al.

The invention of the above listed claims is directed to the step by step synthesis of an array of oligonucleotides in cell locations on a support wherein coupling is directed to certain cells to the exclusion of others via a mask wherein the cell sizes are 10-100 microns. It is noted that the priority date granted for these claims is 5/3/91. It is also noted that this rejection is applied in the event that the above discussed NEW MATTER rejection is overcome.

Fodor et al. discloses the use of masking in a photolithography process to synthesize an array on a solid support as summarized in the abstract, illustrated for peptides in Figure 1 on page 768, and then directed to oligonucleotide synthesis on pages 771-772 starting with the heading "Oligonucleotide synthesis" in the second column of page 771. The basic process of masking and step by set synthesis of sets of cell locations with each monomer type as instantly cited in claim 19 is shown in said Figure 1. Fodor et al. additionally suggests and motivates the oligonucleotide array type for nucleic acid

sequencing on page 772, second column, last full paragraph, to 8-mer arrays with 50 micrometer sites which is within the scope of instant claim 38. A reasonable expectation of success for the synthesis of such arrays is given in Fodor et al. by the synthesis of a dimer array as described in the paragraph that bridges pages 771-772.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to synthesize arrays via masking as instantly claimed because Fodor et al. sets forth the basic synthetic methodology and suggests the oligonucleotide arrays as instantly claimed with an example of a simple oligonucleotide array synthesis which gives a reasonable expectation of success.

Applicant is hereby informed that the prior art made of record as having been considered in the parent application serial number 07/695,682 is also made of record as having been considered in the instant application.

Drmanac et al. is cited on the enclosed PTO Form 892 as of interest in sequencing by hybridization with overlapping multiple oligomeric probes to immobilized target but does not disclose prior immobilization of the probes in an array on a support.

The disclosure is objected to because of the following informalities:

On page 1 of the specification; lines 33, 36, and 37 have been copied poorly such that certain words in each line are lacking certain letters. In line 33, the word after "aspect" is

present as "ap ratus". In line 36, the first word in the line is present as "o gonucleotides". In line 36, the word after "chosen" is present as "len s". In line 37, the first word in the line is present as "p lynucleotide". In line 37, the word after "the" is present as " fferent".

On page 13, lines 17-20, of the specification the yield of oligonucleotides are discussed. The numbers are confusingly inconsistent because it is confusing as to how 2 g of human DNA is equivalent to $\approx 3 \times 10^{-12}$ µmol. If 30 µmol/g is divided into 3×10^{-12} µmol the result is 1×10^{-13} g and not 2 g as given in line 20.

On page 15, line 12, the word "Ccontent" appears to be "C" runtogether with the word "content".

In claim 34, line 2, the word "oligoners" appears to be misspelled.

Appropriate correction is required.

Claims 20 and 36 are allowable over the prior art of record because the prior art of record neither teaches nor suggests the use of a plotter to deliver nucleotides to cell locations for synthesis or applying sample polynucleotides onto an array in strips that are orthogonal to the strips whereon the sequencing oligonucleotides are immobilized.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37

CFR § 1.6(d)). The CM1 Fax Center number is either (703) 305-3014 or (703) 308-4227.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

A. MARSCHEL, Ph.D.

December 21, 1995

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800

12/21/95